JACC Vol. 11, No. 3
March 1988:624–9

Effects of Atrial Natriuretic Peptide on Coronary Vascular Resistance in the Intact Awake Dog

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Atrial natriuretic peptide has been reported to cause vasoconstriction, vasodilation or no change of coronary vascular resistance in isolated perfused hearts or in open chest animal models. Because general anesthesia and acute surgical trauma may perturb baseline coronary hemodynamics and alter responses to experimental interventions, this study examined the effects of human atrial natriuretic peptide (arginine-102–tyrosine-126) and rat atriopeptin II (serine-103–arginine-125) on the coronary circulation of unsedated, awake dogs. Studies were performed in 12 chronically instrumented animals in which a surgically implanted electromagnetic flow probe and intracoronary catheter allowed measurement of left circumflex coronary blood flow during intraarterial administration of the atrial natriuretic peptides.

Bolus doses of both human atrial natriuretic peptide and rat atriopeptin II produced dose-dependent coronary vasodilation; the threshold for coronary vasodilation was 0.2 μg/kg body weight for both agents. Coronary vasodilation produced by human atrial natriuretic peptide was not antagonized by adenosine receptor blockade or by cyclooxygenase inhibition with indomethacin. Thus, atrial natriuretic peptides produced dose-dependent coronary vasodilation in intact awake dogs that was not dependent on adenosine-mediated or prostaglandin-mediated mechanisms.

(J Am Coll Cardiol 1988;11:624–9)

The atrial natriuretic peptides are vasoactive polypeptide hormones that cause relaxation of preconstricted vascular strips (1,2), increase renal blood flow after intraarterial administration (3) and cause decreased forearm vascular resistance in humans (4). However, Wangler et al. (5) reported that atriopeptin II had a profound coronary vasoconstrictor effect in both a Langendorff-perfused guinea pig heart model and in a blood-perfused open chest canine model. In contrast, in a preliminary study (6) we found that intraarterial human atrial natriuretic peptide reduced coronary resistance in a constant flow acute canine model. Burnett et al. (7) found either no effect or transient coronary vasodilation in response to systemic administration of atrial natriuretic peptide to anesthetized dogs as well as in an isolated Langendorff-perfused rat heart preparation.

General anesthesia and acute surgical trauma cause important perturbations of the coronary circulation that may alter responses to subsequent experimental interventions (8). Consequently, this study examined the effects of atrial natriuretic peptide on the coronary circulation in a chronically instrumented, awake canine model. In addition to documenting the response of the coronary circulation to atrial natriuretic peptide, studies were performed to determine whether the vasomotor properties of atrial natriuretic peptide involved adenosine or cyclooxygenase-dependent mechanisms.

Methods

Animal instrumentation and surgical preparation. Twelve adult mongrel dogs weighing 24 to 30 kg were sedated with fentanyl citrate (0.4 mg intramuscularly and droperidol (20 mg intramuscularly), anesthetized with sodium pentobarbital (30 mg/kg intravenously), intubated and ventilated with a respirator. Under sterile conditions, a left thoracotomy was performed in the fifth intercostal space and a 3.0 mm outer diameter heparin-filled polyvinyl chloride catheter was introduced into the left internal thoracic artery and advanced into the ascending aorta. A pericardial cradle was formed and a second catheter was inserted into the left ventricle through the left ventricular apex and tied in place with a purse-string

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Manuscript received June 1, 1987; revised manuscript received August 26, 1987, accepted September 24, 1987.

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0735-1097/88/$3.50

suture. A similar catheter was inserted into the left atrium through the atrial appendage. The proximal left circumflex coronary artery was dissected free and a Howell HSR electromagnetic flowmeter probe (Howell Instruments) was fitted around the artery. A 2.7 mm outer diameter hydraulic occluder constructed of polyvinyl chloride tubing was fitted around the artery distal to the flowmeter probe. Finally, a catheter constructed of a 5 cm length of Silastic tubing with an internal diameter of 0.3 mm bonded to a larger Silastic tubing with an internal diameter of 1.6 mm was introduced into the left circumflex coronary artery just distal to the hydraulic occluder after the method of Gwirtz (9). The pericardium was loosely closed, all catheters and electrical leads were brought out between the ribs, tunneled subcutaneously and exited through the skin at the base of the neck. The dogs were allowed 7 to 10 days to recover before being studied. Catheters were flushed daily with heparin.

Study Protocol

On the day of study, the dogs were placed in a sling and allowed to adjust to laboratory conditions for 1 h before study. Aortic and left ventricular pressures, left ventricular mean rate of pressure rise (dP/dt) and coronary blood flow were recorded continuously on an eight channel direct-writing oscillograph (Hewlett-Packard model 8800). Aortic and left ventricular pressures were obtained using Statham P23ID pressure transducers. Coronary artery blood flow was measured with a Statham SP2202 electromagnetic flowmeter. Flowmeter probes were calibrated in vitro using normal saline solution.

Group I. Group I consisted of eight dogs in which the effect of human atrial natriuretic peptide (arginine-102–tyrosine-126) was studied. Atrial natriuretic peptide was diluted in lactated Ringer solution with bovine serum albumin so that doses of 0.00002, 0.0002, 0.002, 0.02, 0.2, 2.0 and 10.0 μg/kg could be delivered in a volume of 0.5 ml. Doses of atrial natriuretic peptide were injected sequentially into the coronary artery catheter over a period of 5 s and the response was observed. Coronary flow was allowed to return to the preinjection control value before each subsequent injection of atrial natriuretic peptide; at least 1 min was allowed between injections. The response to an equal volume of vehicle was observed before and after the atrial natriuretic peptide responses.

After completion of these control measurements, the effects of adenosine receptor blockade on the response to atrial natriuretic peptide were examined. Adenosine receptor blockade was produced by administration of 8-phenyltheophylline (5 mg/kg intravenously); 10 min after administration, when all pressures and coronary blood flow had returned to baseline values, adenosine receptor blockade was documented by demonstrating at least 95% inhibition of the increase in coronary flow that occurred in response to intracoronary administration of 25 to 50 μg of adenosine. The protocol for administration of graded doses of human atrial natriuretic peptide and vehicle was then repeated. Adenosine receptor blockade was again confirmed after completion of the atrial natriuretic peptide injections. The dogs were then monitored for at least 2 h until adenosine receptor blockade was no longer present as demonstrated by return to control levels of the coronary vasodilator response to adenosine.

Indomethacin (5 mg/kg intravenously) was then administered to determine whether the coronary vasodilation produced by atrial natriuretic peptide involved prostaglandin-dependent mechanisms. Cyclooxygenase inhibition was documented by demonstrating that the increase in coronary flow produced by administration of arachidonic acid (300 to 500 μg as an intracoronary bolus injection) was attenuated after indomethacin administration. The response to atrial natriuretic peptide was again observed after indomethacin.

Group II. The effects of the 23-amino acid rat atriopeptin II (Sigma Chemical) was studied in four dogs in Group II. Atriopeptin II was dissolved in warm 0.05 *M* acetic acid and then diluted in 0.9% sodium chloride so that doses of 0.02, 0.2 and 2.0 μg/kg could be delivered in a volume of 0.5 ml. Bolus doses of vehicle or atriopeptin II were injected sequentially into the coronary artery over 5 s and the response observed as in Group I.

Data analysis and statistics. Aortic and left ventricular pressures and coronary blood flow were measured at the time of the peak response of coronary blood flow to each atrial natriuretic peptide injection. Time to peak flow response and duration of flow response were measured from the onset of injection. Mean coronary vascular resistance was calculated as mean aortic pressure ÷ coronary blood flow. Late diastolic coronary resistance was computed as late diastolic aortic pressure ÷ late diastolic coronary blood flow on a beat by beat basis. Late diastolic pressure and flow measurements were taken at 90% through the cardiac cycle measured from the beginning of the rise of the positive dP/dt tracing. Hemodynamic data before and after each intervention were compared with one-way analysis of variance (ANOVA); when a p value of <0.05 was found, individual comparisons were performed using Duncan's test. Results are presented as mean ± SEM.

Results

Group I

The response to human atrial natriuretic peptide was evaluated in eight dogs and the effects of adenosine receptor blockade with 8-phenyltheophylline and cyclooxygenase inhibition with indomethacin were studied in seven dogs. The effect of atrial natriuretic peptide on late diastolic coronary resistance was assessed in five dogs during control condi-

Table 1. Hemodynamic Data in 8 Awake Dogs During Control Conditions and at the Peak Response of Coronary Flow After Administration of Human Atrial Natriuretic Peptide

ANP (μg/kg)	Heart Rate (beats/min)		Mean Aortic Pressure (mm Hg)		LVEDP (mm Hg)		CBF (ml/min)		Late Diastolic CVR (mm Hg/ml per min)	
	Control	ANP	Control	ANP	Control	ANP	Control	ANP	Control	ANP
Vehicle	104 ± 8	104 ± 9	100 ± 5	101 ± 5	10 ± 2.2	10 ± 2.1	36 ± 3.8	38 ± 4.5	2.75 ± 0.51	2.71 ± 0.48
0.00002	106 ± 10	106 ± 9	103 ± 5	103 ± 4	10 ± 2.1	10 ± 2.3	34 ± 3.2	36 ± 3.3	2.85 ± 0.27	2.81 ± 0.26
0.0002	110 ± 8	109 ± 9	104 ± 4	105 ± 4	7 ± 2.2	7 ± 2.1	35 ± 3.7	39 ± 4.2	2.52 ± 0.45	2.48 ± 0.43
0.002	103 ± 8	103 ± 8	105 ± 4	104 ± 4	10 ± 2.4	10 ± 2.4	36 ± 2.9	40 ± 3.5	2.65 ± 0.66	2.70 ± 0.49
0.02	101 ± 8	100 ± 8	103 ± 4	104 ± 4	10 ± 2.5	10 ± 2.6	35 ± 3.7	42 ± 5.0	2.61 ± 0.36	2.44 ± 0.32
0.2	98 ± 7	97 ± 8	103 ± 4	102 ± 4	10 ± 2.9	10 ± 2.8	35 ± 3.8	43 ± 4.4*	2.73 ± 0.31	2.25 ± 0.23*
2.0	99 ± 7	100 ± 6	102 ± 4	101 ± 4	11 ± 2.4	10 ± 2.3	33 ± 3.4	47 ± 4.3*	2.70 ± 0.25	2.10 ± 0.20*
10.0	95 ± 9	95 ± 9	97 ± 4	96 ± 4	9 ± 3.1	9 ± 3.3	30 ± 3.3	48 ± 4.7*	3.04 ± 0.42	2.02 ± 0.30*

*$p < 0.05$ in comparison with control. ANP = human atrial natriuretic peptide; CBF = coronary blood flow; CVR = coronary vascular resistance; LVEDP = left ventricular end-diastolic pressure. Values are mean ± SE.

tions and after 8-phenyltheophylline administration, and in four dogs after indomethacin administration.

Hemodynamic effects (Table 1). Mean aortic pressure, left ventricular systolic and end-diastolic pressures, left ventricular dP/dt and heart rate did not change after intracoronary injection of vehicle or any dose of human atrial natriuretic peptide (Table 1). Though there was a trend toward a decrease in heart rate and mean aortic pressure during the course of the study, neither achieved statistical significance.

Coronary effects (Table 1, Fig. 1). Mean and late diastolic coronary resistance values were significantly reduced and coronary blood flow was significantly increased by doses of atrial natriuretic peptide ≥0.2 μg/kg. Late diastolic coronary vascular resistance paralleled that of total coronary resistance. The decreases in coronary resistance and increases in coronary flow were directly related to the dose of atrial natriuretic peptide, with a 61% increase in peak coronary blood flow at the highest dose (10 μg/kg). No increase in coronary resistance or decrease in coronary blood flow was observed at any time in response to any dose of atrial natriuretic peptide used in this study. The time to the peak flow response was 5.5 ± 0.3, 7.9 ± 0.5 and 10.4 ± 1.7 s for atrial natriuretic peptide doses of 0.2, 2.0 and 10.0 μg/kg, respectively. The duration of the increase in flow was 14.4 ± 1.3, 20.6 ± 2.1 and 25.6 ± 4.8 s for doses of 0.2, 2.0 and 10.0 μg/kg, respectively.

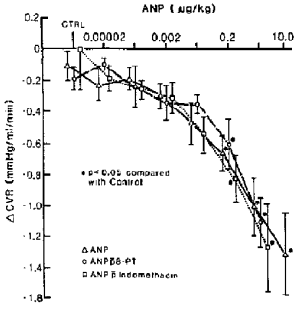

Figure 1. Change in mean coronary vascular resistance (ΔCVR) in response to graded doses of human atrial natriuretic peptide (ANP) during control (CTRL) conditions, after adenosine receptor blockade with 8-phenyltheophylline (8-PT) and after cyclooxygenase inhibition with indomethacin. Values are mean ± SEM.

Adenosine blockade and cyclooxygenase inhibition (Fig. 1). Neither 8-phenyltheophylline nor indomethacin caused a significant change in heart rate, aortic pressure, left ventricular systolic or end-diastolic pressures, coronary blood flow or coronary vascular resistance. The response to atrial natriuretic peptide was not significantly altered by either 8-phenytheophylline or indomethacin. In addition, the time to the peak flow response and the duration of the flow response were not different after 8-phenyltheophylline or indomethacin.

Group II (Table 2, Fig. 2)

Heart rate, mean aortic pressure, left ventricular systolic and diastolic pressures and left ventricular dP/dt did not change significantly in response to any dose of atriopeptin II. Mean and late diastolic coronary resistance decreased significantly at doses of 0.2 and 2.0 μg/kg of atriopeptin II, and coronary blood flow increased 102% at a dose of 2.0 μg/kg. The time to peak flow was 6.4 ± 0.2 and 10.4 ± 2.3 s and the duration of increased flow was 10.9 ± 0.4 and 26.5 ± 6.1 s for doses of 0.2 and 2.0 μg/kg, respectively. No increase in coronary resistance or decrease in coronary blood flow was observed at any time in response to atriopeptin II.

Table 2. Effects of Atriopeptin II on Coronary Blood Flow and Coronary Vascular Resistance in 4 Awake Dogs

Atriopeptin II (μg/kg)	Mean Coronary Vascular Resistance (mm Hg/ml per min)		Late Diastolic Coronary Resistance (mm Hg/ml per min)		Coronary Blood Flow (ml/min)	
	Control	Atriopeptin II	Control	Atriopeptin II	Control	Atriopeptin II
Vehicle	3.01 ± 0.35	3.09 ± 0.36	2.51 ± 0.34	2.54 ± 0.34	37 ± 4.3	37 ± 4.1
0.02	2.94 ± 0.35	2.98 ± 0.2	2.54 ± 0.30	2.60 ± 0.33	38 ± 3.2	38 ± 3.1
0.2	2.99 ± 0.31	2.16 ± 0.33*	2.78 ± 0.38	1.96 ± 0.28*	36 ± 3.1	50 ± 3.9*
2.0	3.17 ± 0.24	1.59 ± 0.11*	2.83 ± 0.36	1.29 ± 0.08*	32 ± 1.7	65 ± 2.6*

*$p < 0.05$ in comparison with control. CTRL = control. Values are mean ± SEM.

Discussion

The intact awake animal model. Vatner and coworkers (8,10,11) demonstrated important differences in the basal level of autonomic nervous system tone and the cardiovascular responses to pharmacologic agents between anesthetized and awake animal models. Anesthetic agents can depress myocardial function, modify regional blood flow and alter reflex control of the coronary vascular bed (8,12–14). Acute coronary dissection can alter coronary vasomotor tone and autoregulatory responses (15). Progressive loss of autoregulation may occur with time in the cannulated, perfused coronary preparation (16). These perturbations may modify responses to subsequent experimental interventions. For this reason, the present study examined the effects of atrial natriuretic peptides on the coronary circulation in chronically instrumented awake animals that were free from the effects of general anesthesia and acute surgical trauma.

Coronary effects of atrial natriuretic peptides. In the awake dog, both human atrial natriuretic peptide and atriopeptin II caused transient dose-related increases of coronary blood flow at doses of ≥0.2 μg/kg. This threshold dose for coronary vasodilation corresponded to a concentration of approximately 80 ng/g of myocardium. Although we (6) previously observed coronary vasodilation in response to human atrial natriuretic peptide in the anesthetized open chest canine preparation with a constant flow coronary perfusion system, the threshold for vasodilation was 100-fold less (0.002 μg/kg) than in the present study, and the duration of the response (up to 180 s) was significantly longer than in the awake animal. Thus, the response to atrial natriuretic peptide was exaggerated in the presence of general anesthesia and acute surgical manipulation.

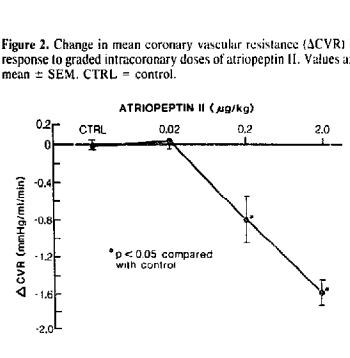

Figure 2. Change in mean coronary vascular resistance (ΔCVR) in response to graded intracoronary doses of atriopeptin II. Values are mean ± SEM. CTRL = control.

Comparison with previous studies. In contrast to the present findings, Wangler et al. (5) reported that atriopeptin II caused only dose-related coronary vasoconstriction in a Langendorff-perfused guinea pig heart preparation. It is possible that these differing results could be related in part to differences in experimental preparation. The vasorelaxant effect of atrial natriuretic peptide on isolated vessel strips is dependent on preconstriction of the vascular smooth muscle (1). In addition, the vasomotor response to atrial natriuretic peptide in the kidney depends on the level of baseline vascular resistance (3). Thus, when baseline vascular resistance was low, atrial natriuretic peptide produced little or no vasodilation, or even a degree of vasoconstriction, in the isolated rat kidney. However, when a high initial level of vascular tone was produced by pretreatment with a vasoconstrictor, atrial natriuretic peptide caused a marked decrease in renal resistance (3).

In the Langendorff-perfused guinea pig heart preparation used by Wangler et al. (5), basal coronary vasodilation is present because the limited oxygen-carrying capacity of the perfusate requires high flow rates. In contrast to this basal coronary vasodilation in the Langendorff preparation, vasomotor tone is high in the intact coronary system. Although coronary vasodilation during basal conditions might impair further vasodilation in response to atriopeptin II, coronary vasodilator reserve was not exhausted in the Langendorff perfusion system used by Wangler et al. (5), as indicated by further vasodilation in response to adenosine infusion. In addition, these investigators also reported that atriopeptin II produced coronary vasoconstriction in an anesthetized open chest blood-perfused canine coronary perfusion system. These results are in contrast to our present findings and those of Burnett et al. (7), who found either no effect or a

modest coronary vasodilator response to intravenous administration of atrial natriuretic peptide in anesthetized dogs. Although differences in experimental preparation may modify the response to atrial natriuretic peptide, they do not adequately explain the differences between our results and those of Wangler et al. (5).

Vasodilator potency. The 25 amino acid human atrial natriuretic peptide (arginine-102–tyrosine-126 atrial natriuretic peptide) and the 23 amino acid rat atriopeptin II (serine-103–arginine-125) were employed in our study. Lack of the C-terminal tyrosine in atriopeptin II has been reported (17) to result in less vasorelaxant activity than occurs with the tyrosine-126–containing human atrial natriuretic peptide. However, in our study, the threshold for coronary vasodilation was similar for the two peptides and there was a tendency for greater vasodilation with atriopeptin II. The plasma concentrations of human atrial natriuretic peptide and atriopeptin II at the threshold dose for coronary vasodilation in our study were estimated to be 1 μg/ml, which is substantially greater than the reported (18) physiologic plasma levels of atrial natriuretic peptide in normal humans (20 to 60 pg/ml) and patients with chronic congestive heart failure (150 to 200 pg/ml). Thus, coronary vasodilation occurred at pharmacologic doses, whereas no response was seen at doses similar to physiologic levels.

Adenosine receptor blockade. Adenosine is a potent endogenous coronary vasodilator. To determine whether it might participate in the coronary vasodilation produced by atrial natriuretic peptide, the coronary blood flow response to human atrial natriuretic peptide was observed after administration of the potent adenosine receptor antagonist 8-phenyltheophylline (19,20). The response to atrial natriuretic peptide was not impaired by adenosine receptor blockade, demonstrating that coronary vasodilation was not mediated through an adenosine-dependent mechanism. Adequacy of adenosine receptor blockade was confirmed by demonstrating marked attenuation of the response to adenosine even at doses that caused greater increases in coronary blood flow than those produced by the highest dose of atrial natriuretic peptide.

Cyclooxygenase inhibition. Coronary vascular tissue can synthesize prostaglandins, and vasoactive arachidonic acid metabolites may contribute to the regulation of coronary flow (21). Cyclooxygenase inhibition has been reported to blunt (22) or have little effect (23,24) on the coronary vasodilator response to hypoxia and ischemia. The effect of cyclooxygenase inhibition was investigated by comparing the response to atrial natriuretic peptide before and after indomethacin. The response to atrial natriuretic peptide was unchanged after indomethacin, demonstrating that coronary vasodilation did not utilize a prostaglandin-dependent mechanism. This finding is consonant with similar results obtained in short-term canine studies (7) as well as in in vitro studies using isolated vascular strips (1).

Conclusions. Both human atrial natriuretic peptide and rat atriopeptin II caused transient vasodilation of the coronary resistance vessels in the intact awake animal; coronary vasoconstriction was never observed. Coronary vasodilation occurred only with pharmacologic doses of atrial natriuretic peptide that produced computed plasma concentrations greater than those previously measured during physiologic conditions. These findings do not support an important role for atrial natriuretic peptide in control of coronary blood flow.

We acknowledge the expert technical assistance provided by Eugene Sublett, Terry Nesbitt and Paul Lindstrom. Secretarial assistance was provided by Frank Kane and Annette Dear. Human atrial natriuretic peptide was generously provided by Rodney W. Lappe, PhD, of Wyeth Laboratories, Philadelphia, Pennsylvania.

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